

REMARKS

Claims 3-9 and 25-29 are presently pending. Entry of the foregoing amendments and favorable reconsideration of the present application is respectfully requested in view of the following remarks.

The rejection of Claims 4, 9, 25 to 27 and 29 under 35 U.S.C. §112, first paragraph (enablement), is respectfully traversed.

The Examiner relies on several references in an attempt to support her assertion that a malaria vaccine is not enabled in the present specification. However, for the reasons detailed below, many of these references are irrelevant with respect to the presently claimed invention.

First of all, the Examiner relies on the articles of Arevalo-Herrera et al and Shi et al to demonstrate that the art teaches that only multi-stage and multi-component vaccines are feasible as malarial vaccines due to the complexity of the parasite's life cycle. However, **enclosed** Document I details numerous on-going clinical trials of malaria vaccines in which non-multi-stage vaccines are actually in use, contrary to the assertion by the Examiner. More specifically, enclosed Document I reflects the state of the vaccine art and demonstrates that non-Multistage vaccines are currently in clinical trials. Therefore, Document I is more reflective of the vaccine art as of the date of the present invention than the articles relied upon by the Examiner, which are research articles and reviews (past state of the art).

Furthermore, Arevalo-Herrera et al and Shi et al do not reflect the state of the art with respect to MSP-3 peptides. This is evidenced by the fact that Shi et al do not even mention MSP-3 peptides and Arevola-Herrera et al do not provide any details about these peptides, but only mention that MSP-3 peptides exist.

In addition to the above, on pages 4-6 of the Official Action mailed March 25, 2005, the Examiner relies on several references that describe LSA peptides and antigens. LSA is a liver-stage antigen, which is a different stage antigen than the merozoite surface protein 3 antigens of the present invention, which are blood-stage antigens. The Examiners reliance on references, in the liver-stage antigen literature in this rejection is unfounded since it is directed to a *different stage* than the blood-stage and these antigens work by entirely different mechanisms. The skilled artisan would readily appreciate that only art related to the specific parasitic stages is relevant and would not rely on the disclosure in the art from other malaria parasitic stages.

Moreover, it appears that the Examiner's position is that a vaccine has to provide protection and that stimulation of an immune response does not equate to vaccine protection. However, although the MSP-3 peptides of the present invention have B and T epitopes, these peptides also block the division of intraerythrocytic parasites, which is a clear indication of parasite killing, as demonstrated by the ADCI experiments set forth in the specification (see Examples 10-11). Indeed, the demonstration of ADCI provides a means of generating cross-strain protection, since macrophages activated by antibodies to one variant can kill parasites in red blood cells of other strains and variants of *P. falciparum*. Moreover, ADCI can continue after merozoite invasion and entry into the red blood cells.

Furthermore, the Examiner has not commented on the impact of attaining parasitic killing with the MSP-3 peptides set forth in the present specification in rendering this rejection and why such a demonstration would not rise to the level of a vaccine. Thus, Applicants submit that the Examiner has not met her burden of establishing a *prima facie* case of lack of enablement.

To further substantiate the enablement of the present application, Applicants submit herewith a Declaration under 37 C.F.R. §1.132 executed by Mr. Pierre Druilhe (the Druilhe

Declaration). The Druilhe Declaration and the specification clearly demonstrate that the MSP-3 long synthetic peptides of the present invention are able to elicit antibodies in humans when administered in low doses with alum or Montanide® that are able to kill the *P. falciparum* parasite or inhibit the growth of the parasite. Thus, Applicants' submit that the specification *has enabled* the claimed invention.

In view of the foregoing, withdrawal of this rejection is respectfully requested.

The rejection of Claims 3-7 and 25-27 under 35 U.S.C. § 102 (b) over Oeuvray et al. (Blood 1994) or Oeuvray et al. (Mem. Inst. Oswaldo Cruz, Rio de Janeiro; Supp. II 1994) is respectfully traversed.

Oeuvray et al (Blood) do not disclose SEQ ID NO: 13 or SEQ ID NO: 14, the latter of which is an MSP-3d peptide and combinations thereof. As such, this reference clearly cannot anticipate the claimed invention.

There is no disclosure of SEQ ID NO: 14 in this reference. With respect to SEQ ID NO: 13, in the present invention this sequence ends with an Asp, while in Oeuvray et al (Blood), the sequence ends with a Glu. Applicants submit that this change in amino acid makes the overall sequence structurally distinct, since there are structural differences between Glu and Asp, the former having an additional CH₂ group in its structure. The Examiner has not taken into consideration that there are structural differences between the peptides of MSP-3c described in the Oeuvray et al references and that of the present invention.

Moreover, the Examiner's belief that the sequences disclosed by both references of Oeuvray "appear that they are the same or an obvious variant" cannot be maintained in this novelty rejection, since the sequences are *not the same* as demonstrated above and "an obvious variant" is not the criteria set forth in the law for a novelty rejection. This is clear from the case of *Pacifica Technics Corp. v. United States*, 11 Cl. Ct. 393, 408, 3 USPQ2d

1168, 1178 9CL. Ct. 1986) aff'd in part, vacated in part, 385 F.2d 871 (fed, Cir. 1987)

(unpublished) where the court stated the following:

The ...Federal Circuit has determined that if the general aspects are the same and the differences in minor matters are only such as would suggest itself to one of ordinary skill in the art, a prior art disclosure that 'almost' meets the standard may render the claim invalid under Section 103, but does not 'anticipate' the claimed invention under Section 102.

Moreover, Oeuvray et al. (Blood) disclose the person skilled in the art that antibodies directed only to the MSP-3b, but not to MSP-3a and MSP-3c were detected by ELISA in 8 out of 10 hyperimmune sera. Due to these results only MSP-3b was further analyzed in mice and proved to be immunogenic when injected alone without a carrier molecule, as specifically stated at page 1600, 2nd column before the discussion:

Antibodies directed to peptide MSP-3b, but not to MSP-3a and MSP-3c were detected by ELISA in 8 of 10 hyperimmune sera studied (data not shown). Peptide MSP-3b was used to immunize outbred mice and proved to be immunogenic **when injected alone without carrier molecule**. Both the sera from these mice as well as human antibodies immunopurified on peptide MSP-3b were found to be able to recognize the parasite protein in IFA and Western blots (Fig. 3A, lanes 2 and 3), demonstrating that the peptide mimicked properties the epitopes defined by the native protein (emphasis added).

Therefore, in view of the disclosure that the MSP-3b peptide was injected alone Claim 4 cannot be anticipated by Oeuvray et al (Blood) since there is no disclosure of a pharmaceutical carrier.

With respect to Claim 7, there is no disclosure in Oeuvray et al (Blood) of an immunogenic composition comprising 3 µg to 100 µg of a long synthetic peptide.

Oeuvray et al (Mem. Inst. Oswaldo Cruz, Rio de Janeiro, Supp. II 1994), hereinafter referred to Oeuvray, et al (Supp II) do not disclose SEQ ID NO: 13, SEQ ID NO: 14 nor combinations of SEQ ID NO. 13 and SEQ ID NO:14. As stated above, with respect to Oeuvray et al (Blood), the amino acid sequence of MSP-3c in Oeuvray et al (Supp II) ends in

a Glu, while the sequence in the present invention ends in an Asp. Thus, there is a structural difference.

Furthermore, like the previous reference of Oeuvray et al (Blood), the present document discloses that only the MSP-3b peptide proved to be immunogenic as discussed in the paragraph bridging pages 79 and 80 and set forth below:

Peptide MS;P-3b was used to immunize outbred mice and proved to be immunogenic **when injected alone without carrier**. Sera from mice as well as human antibodies affinity purified on peptide B (Brahimi et al. 1993), were found able to recognize the parasite protein IFA and western blots (emphasis added).

For the same reasons set forth above with respect to Oeuvray et al (Blood), Claim 4 cannot be anticipated by Oeuvray et al (Supp. II) since there is no disclosure of a pharmaceutical carrier.

With respect to Claim 7; there is no disclosure in Oeuvray et al (Supp. II) of an immunogenic composition comprising 3 µg to 100 µg of a long synthetic peptide.

Therefore, Applicants submit that the presently claimed invention is not anticipated by Oeuvray et al (Blood) or Oeuvray et al (Suppl. II).

Accordingly, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 3 and 5-8 under 35 U.S.C. §103 (a) over Oeuvray et al (Blood) or Oeuvray et al (Suppl. II) taken with Saul et al is respectfully traversed.

The presently claimed invention is directed to new chemical entities having a different structure than those of the cited prior art (i.e., different structural features as set forth above in the response to the novelty rejection in view of the cited Oeuvray documents).

The issue that needs to be addressed in this obviousness rejection is whether the prior art would have suggested to a person skilled in the art to make the specific molecular

modifications necessary to achieve the same claimed compounds. See, In re Jones, 958 F. 2d 347, 351, 21 USPQ2d 1941, 1944 (Fed. Cir. 1992).

There is no disclosure or suggestion neither in Oeuvray et al (Blood) nor in Oeuvray et al (Suppl. II) to modify any of the sequences disclosed therein to arrive at the MSP-3 sequences as presently claimed. Indeed, the skilled artisan would realize from the disclosures of these two primary references that the MSP-3b peptide was in fact the only peptide tested for immunogenicity.

Saul et al do not remedy the deficiencies of the primary reference, since the specifically claimed MSP-3 sequences are not disclosed or suggested in Saul et al. Indeed, the peptides used in Saul et al are a full length MSP-2 peptide, a 175 amino acid fragment of an MSP-1 peptide and a C -terminal 70% RESA peptide. However, there is simply no disclosure or suggestion to motivate the skilled artisan to use or modify MSP-3 sequences, to arrive at those sequences, which are currently claimed.

Since neither reference discloses nor suggests the MSP-3 peptides of the present invention or how to modify those MSP-3 peptides to arrive at the presently claimed peptides, Applicants submit that this obviousness rejection cannot be maintained.

Thus, in view of the foregoing, withdrawal of this rejection is respectfully requested.

The rejection of Claims 28 and 29 under 35 U.S.C. § 112, second paragraph, is obviated by amendment.

Applicants have amended Claims 28 and 29 to address the Examiner's criticisms. As such, this ground of rejection is believed to now be moot.

Withdrawal of this ground of rejection is requested.

Application Serial No. 10/774,602
Reply to Office Action of March 25, 2005

Applicants submit that the present application is in condition for allowance. Early notification to this effect is respectfully requested.

Respectfully submitted,

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(OSMMN 08/03)

Portfolio of candidate malaria vaccines currently in development February 2004

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Activities completed or ongoing are marked with a bold X
Support for activities indicated with colour and without an X have been secured
The various stages are considered as initiated at the steps indicated below:
Preclinical development stage: serious process development has been initiated
Phase 1a: first volunteer recruited for phase 1 in industrialized country
Phase 2a: first volunteer recruited for challenge study in industrialized country
Phase 1b: first volunteer recruited for phase 1 in disease endemic country
Phase 2b: first volunteer recruited for phase 2 in disease endemic country
Pivotal: first volunteer recruited for clinical study leading to licensure

Pre-erythrocytic vaccines

	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
CSP							
HBSAg-CSP chimeric mixed VLP (RTS,S)/AS02A (GSK)	X	X	X	X			
HBSAg-CSP chimeric mixed VLP (RTS,S)/AS02A and (RTS,S)/AS01B (WRAIR/GSK)	X	X	X	X			
HBCAg-CSP VLP (Malarivax Apovia)							
Modified Vaccinia Ankara (MVA) CSP tested in combination with RTS,S/AS02 (Oxford-GSK)	X						
Recombinant adenovirus CSP (NYU)							
Recombinant adenovirus CSP (WRAIR/Crucell Holland)	X	X					
Recombinant influenza CSP (NYU)							
Recombinant vaccinia CSP (NYU)							
Recombinant Sindbis virus CSP (NYU)							

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Pre-erythrocytic vaccines – CSP (continued)	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Recombinant Yellow Fever virus CSP (NYU)	X						
Long synthetic CSP peptide (Lausanne)	X	X	X	X			
CSP DNA immunization (NMRC)	X	X	X				
Long Vivax CSP C-terminus 72 AA Synthetic peptide (MVDC)	X	X	X				
Long Vivax CSP N-terminus 77AA Synthetic peptide (MVDC)	X	X	X				
Long Vivax CSP repeat 48 AA Synthetic peptide (MVDC)	X	X	X				
Other antigens							
Long synthetic LSA-3 peptide (Pasteur Institute)	X	X					
<i>L. lactis</i> expressed recombinant LSA-3 protein + lipopeptides (Institut Pasteur)	X	X					
<i>E. coli</i> recombinant LSA-3 (WRAIR)	X						
<i>E. coli</i> recombinant LSA-1 (LSA-NRC) (WRAIR)	X	X					
Adenovirus vectored LSA-1 (LSA-NRC) (WRAIR/Crucell Holland)	X	X					
Modified Vaccinia Ankara (MVA) CSP + LSA-1 epitope (Oxford)							
Fowl Pox 9 CSP + LSA-1 epitope (Oxford)							
Fowl Pox 9 CSP + LSA-1 epitope/ Modified Vaccinia Ankara (MVA) CSP + LSA-1 epitope (Oxford)	X	X					
DNA MVA prime-boost Multi-epitope (ME) string + TRAP (Oxford)							
Fowl Pox 9 MVA prime-boost ME string + TRAP (Oxford)							

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Pre-erythrocytic vaccines – CSP (continued)		Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Recombinant BCG-vectored vaccine CSP + 2 additional pre-erythrocytic antigens (Towson State University)							
<i>Drosophila melanogaster</i> recombinant LSA-1 (Hawaii Biotech, Inc.)							
Multi- pre-erythrocytic epitope DNA vaccination (Epimmune/NMRC)	X						
Attenuated <i>P. falciparum</i> sporozoite vaccine (Sanaria)							

Blood Stage vaccines

	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
MSP-1							
<i>E. coli</i> expressed MSP-1 19kD recombinant protein (ICGEB)	X	X					
<i>E. coli</i> expressed MSP-1 42kD recombinant protein (ICGEB)	X	X					
Recombinant full length MSP-1 3D7 (Heidelberg/WRAIR)	X	X					
Recombinant full length MSP-1 FCB1 (Heidelberg/WRAIR)	X	X					
Recombinant full length MSP-1 3D7 + FCB1 (Heidelberg/WRAIR)	X	X					
Baculovirus recombinant protein MSP-1 19kD (Pasteur Institute)	X	X					
Baculovirus recombinant protein MSP-1 42kD FUP (U of Hawaii/Antigenics)	X	X					
Transgenic mammals expressed MSP-1 42 FVO (GTC Biotherapeutics/SAIC)							
<i>P. Pastoris</i> recombinant protein MSP-1 19kD mutant (Mill Hill)	X						
<i>E. coli</i> expressed recombinant protein MSP-1 42Kd 3D7 (FMP-1)(WRAIR)	X	X	X	X			
<i>E. coli</i> expressed recombinant protein MSP-1 42Kd FVO (FMP-9)(WRAIR)	X	X					

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Blood Stage vaccines – MSP-1 (continued)	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
<i>P. pastoris</i> expressed recombinant protein MSP-1 42Kd 3D7 (MVDU)							
<i>P. pastoris</i> expressed recombinant protein MSP-1 42Kd FVO (MVDU)							
<i>P. pastoris</i> recombinant AMA-1 and MSP-1 chimera (SMMHS)	X	X	X				
<i>E. coli</i> recombinant MSP1-42-kDa-EBA-175 chimera (WRAIR)	X	X					
<i>E. coli</i> expressed recombinant MSP1-19 and EBA-175 F1 domain protein (ICGEB)	X	X					
<i>D. melanogaster</i> expressed MSP1 19 kD protein (Hawaii Biotech, Inc.)							
<i>D. melanogaster</i> expressed MSP1 42 kD protein (Hawaii Biotech, Inc.)							
BCG vectored MSP-1 (AECOM)							
<i>Salmonella</i> -vectored MSP-1 (U. Maryland)							
Other MSPs							
Long synthetic peptide MSP-2 (Lausanne)	X	X					
<i>E. coli</i> expressed recombinant protein MSP-2 3D7+ (FC27) (La Trobe)	X						
Long synthetic peptide MSP-3 (Pasteur Institute)	X	X	X		X		
<i>E. coli</i> expressed recombinant MSP-4 protein (Monash)	X						
<i>E. coli</i> expressed recombinant MSP-5 protein (Monash)	X						
MSP-3-GLURP hybrid vaccine (SSI)	X	X	X		X		
AMA-1							
<i>E. coli</i> recombinant protein AMA-1 (Australia)	X	X	X				
<i>E. coli</i> expressed recombinant protein AMA-1 3D7 (MVDU)							

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Blood Stage vaccines – AMA-1 (continued)	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
<i>E. coli</i> expressed recombinant protein AMA-1 FVO (MVDU)							
<i>P. pastoris</i> expressed recombinant AMA-1 protein (BPRC)							
<i>E. coli</i> recombinant protein AMA-1 FVO (FMP10)(WRAIR)							
<i>E. coli</i> recombinant protein AMA-1 3D7 (FMP2.1)(WRAIR)							
EBA-175 and DBP							
<i>E. coli</i> expressed recombinant Region II Duffy Binding Protein protein (ICGEB)							
<i>E. coli</i> expressed recombinant EBA-175 F1 domain protein (ICGEB)							
<i>P. pastoris</i> recombinant protein EBA-175 (F1 +F2) (EntreMed/SAIC)							
Other proteins							
Long synthetic GLURP peptide (SSI)							
MAEBL (Notre Dame University)							
<i>P. Pastoris</i> expressed erythrocyte binding proteins EBP2/BAEBL (Entremed)							
<i>E. coli</i> expressed recombinant RAP-2 protein (QIMR)							
<i>E. coli</i> , <i>P. pastoris</i> , baculovirus expressed PfEMP1, different domains (various EU groups)							
<i>P. falciparum</i> synthetic GPI toxin (WEHI/MIT)							

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5

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Transmission blocking vaccines

	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
<i>Saccharomyces</i> recombinant protein PvS25 (MVDU)							
<i>P. Pastoris</i> recombinant protein PfS25 (MVDU)							
Recombinant protein PfS48 (MVDU)							
Recombinant protein PfS48 (Nijmegen)							
DNA immunization PfS25 (JHU)							
DNA immunization PvS25 (JHU)							
DNA immunization PvS28 (JHU)							
Recombinant Pfs230 (Loyola University)							

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6

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Combination (Multistage) Vaccines

	Research	Preclinical development	Phase 1a	Phase 2a	Phase 1b	Phase 2b	Pivotal
Multi-epitope recombinant protein CSP, MSP-1, MSP-2, LSA-1, AMA-1, RAP-1, EBA-175 (FALVAC CDC)	X						
MVA prime-boost Fowl Pox 9 LSA3/D260; STARP; EXP1, Pfs16, TRAP, LSA-1 (Oxford)	X	X					
DNA in co-block polymer +/- viral boost CSP, SSP2, LSA-1, AMA-1, MSP-1 (NMRC)	X	X					
MVA CSP, SSP2, LSA-1, AMA-1, MSP-1 (NMRC)	X	X					
Recombinant <i>Salmonella</i> -vectored vaccine CSP, SSP2, LSA-1, MSP-1, individually as well as in combination (U Maryland)							
Recombinant <i>Shigella</i> -vectored vaccine CSP, SSP2, LSA-1, MSP-1, individually as well as in combination (U Maryland)							
Multivalent antigen expression/vaccine for malaria (Lifesensors, Inc.)							
Recombinant Adenovirus CSP, SSP2, LSA-1, AMA-1, MSP-1 (NMRC/Genvec)	X	X					
Recombinant FMP-1 plus RTS,S, MSP-1 3D7 + CSP (WRAIR)	X	X	X				
Mimetopes delivered on Virosome CSP, MSP-1, AMA-1 (Pevion)	X	X					

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